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EDITORIAL COMMENT

The Less Familiar Face of Heart Failure*

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Nearly five million Americans have heart failure (HF) today, an incidence approaching 10 per 1,000 population after the age of 65 years. Heart failure is the reason for at least 20% of all hospital admissions in persons above the age of 65 years; hospitalizations for HF have increased by 159% (1). Substantial efforts have been made to identify and treat those factors that predict recurrent hospitalization for HF, in addition to the identification of therapies that improve overall survival. Indeed, over the past decade, multiple clinical trials have unequivocally demonstrated a significant reduction in mortality for patients with systolic HF. Simultaneously, however, large epidemiologic or cohort registries have not observed an equivalent impact on overall death rates from HF (2–4). Clearly, as has been noted by a number of investigators, the patients entered into recent clinical trials of HF have not been entirely representative of the "typical" patient with HF in the U.S. (5).

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It is in the context of a further description of patients with HF who are utilizing our hospitals that the study by Masoudi et al. (6) in this issue of the *Journal* is of great interest. They abstracted charts from 37,500 Medicare beneficiaries hospitalized primarily for HF from the National Heart Failure Project (NHF) database. They report three important observations.

1. Only 57% of patients had an assessment of left ventricular function to determine ejection fraction (EF) during their index hospitalization. Guidelines for the management of HF have outlined the need for a measurement of ventricular function since 1994 (7).
2. Of the 19,710 patients with a documented EF, 66% had HF associated with systolic dysfunction. Approximately a third of all patients had HF with a preserved EF (an EF of ≥50% in this study), a syndrome that has been termed diastolic HF (8,9).
3. Diastolic HF was present almost twice as frequently in women as in men. This correlation was consistent across a wide range of patient characteristics, including age and etiology of cardiac disease.

These investigators are not the first to report the higher prevalence of diastolic HF in elderly women, as the authors acknowledge in their discussion. Likewise, the incidence of diastolic HF in hospitalized patients is also not a new observation. However, this analysis comprises a several-fold higher number of patients than previous studies, and Masoudi et al. (6) have attempted to eliminate potential flaws or biases of previous, smaller studies.

There are a number of implications in these data, some of which have been emphasized by the authors. Table 1 depicts the age and gender characteristics of some representative cardiovascular trials, the majority of which were multicenter, randomized studies involving patients with systolic dysfunction (10–18), with or without (19–22) symptomatic HF. Other studies depicted in Table 1 examine the cause of unexplained cardiomyopathy (23), or those factors that best predict survival after the onset of HF (24). Two pivotal trials examining the impact of intervention in high-risk populations with vascular disease or acute coronary syndromes are also included (25,26). The mean age of the populations studied was usually <65 years, and women were typically underrepresented. (The number of women from races other than Caucasian is not usually reported.) Even in trials structured to investigate the response of an older population (14), or in cardiovascular syndromes such as aortic stenosis (27), often associated with elderly women, fewer than half of the participants were female. It is only in the large population-based studies that the natural history of the elderly and women has been explored (2,4,28–30).

Is there any reason to think that elderly patients or women respond differently to therapy for HF? Several studies in Table 1 noted a prognostic impact of age, so that clinical outcome worsened as patients advanced in years (4,23,27). The impact of age on decisions to proceed with thrombolysis or catheter-based intervention after myocardial infarction has become important as a result of clinical trials including very elderly patients. Management algorithms for patients with cardiomyopathy, with or without symptoms, may also need to consider age as a valuable determinant, especially when the cost of defibrillators or ventricular assist devices may be applied. Elderly patients tend to have a higher prevalence of comorbidities, and an increased incidence of adverse effects to medications, in addition to the altered pathophysiology of the aging myocardium and conduction system (31–33).

A growing body of literature suggests that there are gender differences in the biologic response to chronic hypertension, pressure overload such as seen in aortic stenosis, and myocyte loss after myocardial infarction (34). Hypertension and diabetes seem to confer a greater risk of HF for women compared to men, despite the usual finding of less coronary disease in females (35). Conclusive data for the reduction of mortality and morbidity after angiotensin-converting enzyme inhibition exist only for men with HF; beta-blockers appear to be effective for both genders with systolic dysfunction and symptoms of HF (36). Everything

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Table 1. Age and Gender Characteristics of Representative Heart Failure or Cardiovascular Trials

Study, Year (Ref.)	Purpose of Study/End Point	# of Patients	Mean Age (yrs)	Women	Comments
SOLVD, 1991 (19)	ACEI in HF; mortality	2,569	61	20%	no gender or age difference observed in primary result
PROMISE, 1991 (10)	Oral inotrope in HF; mortality	1,088	64	22%	no gender or age difference observed in primary result
DIG, 1997 (11)	Digoxin in HF; mortality	6,800	63	22%	no gender or age effect on primary outcome
RALES, 1999 (12)	spironolactone in HF; mortality	1,663	65	27%	no gender or age difference observed in primary result
ATLAS, 1999 (13)	Dose effect of ACEI in HF; mortality	3,164	64	20%	gender or age effect not reported
ELITE II, 2000 (14)	ARB versus ACEI in HF; mortality	3,152	72	30%	no gender or age difference observed in primary result
Unexplained Cardiomyopathy, 2000 (23)	Examine cause of new onset HF	1,230	48	40%	female gender had better prognosis overall; increasing age had worse prognosis
Val-HeFT, 2001 (15)	ARB in HF; mortality	5,010	63	20%	no gender or age difference observed in primary result
BEST, 2001 (16)	Beta-blocker in HF; mortality	2,708	60	22%	no gender difference in primary outcome; age effect not reported
COPERNICUS, 2001 (17)	Beta-blocker in HF; mortality	2,289	63	20%	no gender or age difference observed in primary result
CIBIS II, 2001 (18)	Beta-blocker in HF; mortality	2,647	Women—65; men—60	19%	female gender had better prognosis; increasing age had worse prognosis
HFSS Score, 1997 (24)	Risk stratification in HF	467	51	20%	gender or age not important in risk profile
STAT-CHF, 1995 (20)	Amiodarone in HF and PVCs; mortality	674	65	1%	gender or age effect not reported
CABG Patch, 1997 (21)	ICD in EF $<$ 36% at CABG, abnormal signal average; mortality	1,055	64	16%	gender or age effect not reported
Outcome in Aortic Stenosis, 2000 (27)	Predictors of outcome in severe, asymptomatic AS	128	60	45%	no gender effect on outcome; increasing age had worse prognosis
HOPE, 2000 (26)	ACEI in vascular disease ± diabetes; composite	9,297	66	27%	no gender or age effect on primary outcome
MIRACL, 2001 (25)	Statin after ACS; composite	3,086	65	35%	no gender or age effect on primary outcome
CAT, 2002 (22)	ICD in EF $\leq$ 30%; mortality	104	52	20%	no gender or age effect on primary outcome
Strong Heart Study, 2000 (28)	Prevalence of DHF	3,638	62	~64%	DHF more often in older women
Scotland population, 2000 (4)	Mortality in hospitalized patients with all CHF	66,547	75	53%	age and gender had impact on mortality
Testing in DHF, 2001 (30)	Clinical utility of EF	63	58	35%	
Framingham Heart, 2002 (29)	Risk of hypertension	1,298	Baseline: 55–65	54%	no effect of age or gender on risk

ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blockade; AS = aortic stenosis; CHF = both systolic and diastolic dysfunction leading to heart failure; CABG = coronary artery bypass grafting surgery; DHF = diastolic heart failure; EF = ejection fraction; HF = heart failure secondary to systolic dysfunction (EF $<$ 40%); ICD = implantable cardio-defibrillator; PVCs = premature ventricular contraction.

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from apoptosis to arrhythmias appears to exhibit gender-specific characteristics.

If diastolic HF is often a disease of elderly women (8,9), and we have little information acquired from clinical trials to date about the elderly or about women, it should not be unexpected that there is a mounting sense of urgency to become more familiar with this group of patients (37). To make a meaningful dent in the cost to our economy from HF admissions, we are obligated to begin clinical trials in patients with diastolic HF. Federal efforts to increase the representation of women in clinical trials have been moderately successful, primarily because of a small number of large, single-gender trials involving coronary disease. There has been little change in the gender composition of cohorts in the majority of other studies of cardiovascular disease (38). This could change dramatically if we started to enroll subjects in a trial on diastolic HF.

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